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REVIEW ARTICLE

Interstitial Implantation Techniques in Prostate Cancer

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Brachytherapy is a radiotherapeutic technique that allows the physician to implant radioactive isotopes into a body cavity or directly into tissue. Different radioisotopes have unique characteristics that the brachytherapist may utilize for a particular situation. The use of brachytherapy is part of standard radiation oncology practice in gynecological and head and neck cancer management. The prostate is approachable for interstitial implantation due to its close proximity to the perineum. Over 20 years ago, primitive methods of brachytherapy were utilized in the treatment of prostate cancer. However, poor results due to inconsistency in achieving adequate coverage of the entire prostate and poor patient selection caused this treatment modality to fall out of favor. Technological advances over the last decade have restored attention to brachytherapy for prostate cancer. Particularly important has been the development of transrectal ultrasound, new radioisotopes such as palladium-103, computer tomography, computerized dosimetry systems, and earlier diagnosis. Modern interstitial implantation utilizing transperineal template and transrectal ultrasound guidance has resulted in improved consistency in radiation dose delivery to the entire prostate. Early results are encouraging in terms of the relatively low morbidity of the procedure, improved local control rates, and biochemical progression free survival. This has resulted in an outpatient treatment that has high patient acceptance.
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KEY WORDS: brachytherapy; palladium-103; iodine-125; high dose rate

INTRODUCTION

Today, prostate cancer is the second most common malignancy of men. The absolute incidence is rising at an average of >8% per annum [1]. The prostate-specific antigen (PSA) blood test has helped to increase the proportion of early stage disease at time of diagnosis. Currently, 77% of patients are found to have early stage disease at time of diagnosis, as compared to only 57% between 1975 and 1979 [2].

The uncertainty of the clinical significance of early stage disease detected by PSA has led to much debate in the medical, political, and business communities. Critics of aggressive therapy state that the morbidity of external beam radiation therapy and radical prostatectomy may not be justified due to uncertain survival benefits of definitive therapy of early stage disease [3–5]. Expectant management of early stage disease, particularly in older men, is recommended as another option [1,5,6].

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What is clear, however, is that >240,000 men will be diagnosed with prostate cancer and >40,000 will die of the disease this year [7]. The high incidence of early stage disease has increased the percentage of patients that are appropriate candidates for interstitial brachytherapy. Technological advances over the last 10 years have improved the accuracy of both permanent and temporary interstitial implantation of the prostate [8–25]. The renewed interest in brachytherapy is thus a result of improvements in computer dosimetry, patient selection, transrectal ultrasound technology, transperineal template guidance systems, improved imaging technology, and new radioisotopes (palladium-103). Brachytherapy is now a definitive treatment option for early stage prostate cancer. The modern brachytherapy techniques, principles, results, and theoretical advantages and disadvantages of various techniques are reviewed.

HISTORICAL OVERVIEW

Brachytherapy is one of the oldest forms of radiation therapy. Denning [26] in 1922, reported on the transurethral insertion of radium in 100 patients with carcinoma of the prostate. At that time there was no reliable way to measure absorbed radiation dose. Not surprisingly, the complication rate was high, but the local control rate was relatively good. Brachytherapy fell into disuse with the introduction of radical prostatectomy and improved anesthetic and surgical techniques. In the 1960s, radiation therapy became popular in the treatment of prostate carcinoma with the development of megavoltage external beam radiation.

Brachytherapy was reintroduced by Scardino and Carlton [27] in the 1960s. They combined external beam radiation and interstitial implantation of gold 198 [27]. The open laporatomy retropubic permanent interstitial iodine seed implant (Fig. 1) was developed by Whitmore et al. [28] in the early 1970s at Memorial Sloan-Kettering Cancer Center in New York City. These techniques of prostate brachytherapy were quite popular for a time. However, these implants were essentially placed freehand into the prostate. Patients with significant transurethral resection (TURP) of the prostate defects and stage C patients were implanted. Although a spacing nomograph was developed, sophisticated, computerized three-dimensional preplanning was not available [29]. The evaluation of the accuracy of the implant was not possible due to the limitation of the technology in that era. Results were mixed, and once again brachytherapy fell into disfavor.

In the 1980s, several technological advances occurred. Open retropubic-transperineal, template-guided temporary iridium implantation was pioneered by Puthawala et al. [30]. Martinez et al. [31] combined external beam radiation and multiple-site perineal applicator for the treatment of locally advanced prostate cancer. In 1983, Holm et al. [8] published their technique of transperineal closed permanent ultrasound guided iodine 125 seed implantation of the prostate. Modifications of this method are currently being utilized to guide both permanent and temporary interstitial implants (Fig. 2) [9,13,16, 17,23,32]. Improved patient selection, sophisticated computerized preplanning, post-implant dosimetry evaluation, and new radioisotopes are further advances that occurred in the mid-1990s.

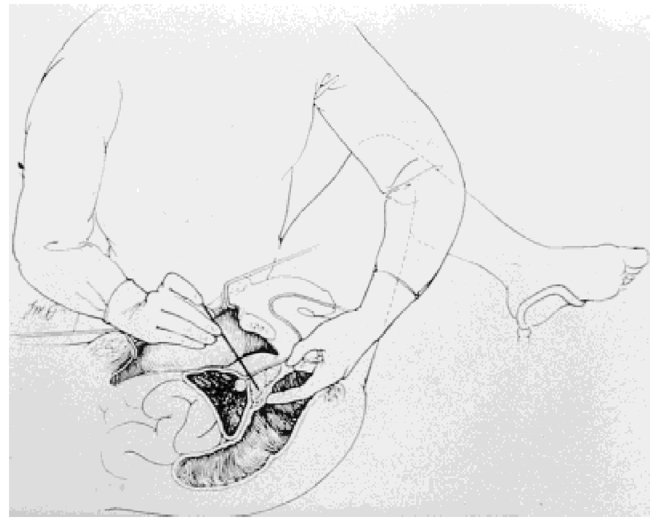

Fig. 1. Open retropubic permanent interstitial seed implantation technique.

MATERIALS AND METHODS

Modern brachytherapy utilizes either temporary or permanent interstitial radioactive implantation. In permanent implantation the radioactive isotopes are left permanently in the prostate. The radioisotope, or seed, delivers its radiation dose by radioactive decay, eventually leaving an inert metal pellet. Most centers use either iodine-125 or palladium-103. These isotopes have a low energy (28 KeV and 21 KeV, respectively), which limits the depth of tissue exposed, such that the prostate and ~5 mm beyond are treated. This has the advantage of lowering the dose that uninvolved normal surrounding tissues such as the rectum and bladder, receive, but also limits its usefulness to early stage disease.

Temporary implantation utilizes iridium-192. This has a higher energy, thus penetrating deeper beyond the prostate. This source is left in place in the prostate for a specific calculated time of exposure, then removed. Theoretically this would allow the treatment of more advanced stage disease (T3); however, this method delivers a higher dose to the normal surrounding uninvolved tissue.

Currently most centers that perform either permanent

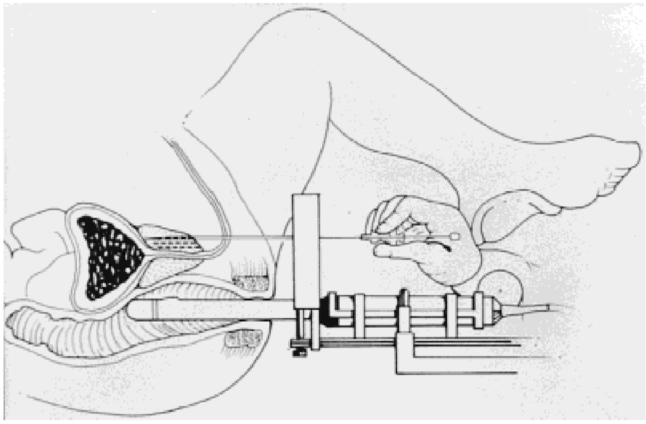

Fig. 2. Modern closed transperineal ultrasound-guided seed implantation technique.

or temporary interstitial implantation use the closed nonsurgical transperineal approach. Both methods utilize template guidance and transrectal ultrasound or computer tomography guidance. Each method has certain theoretical and practical advantages and disadvantages.

Modern Permanent Interstitial Implantation

The 1980s witnessed the introduction of closed transperineal template guidance systems, transrectal ultrasound technology, and computerized treatment planning systems. There were advances in physics and radiobiology that improved our understanding of dose rate deposition versus cancer growth rates, and how cell kill could be influenced by dose rates. There is evidence that rapidly dividing cells may be able to outgrow low dose rate radiation therapy [33,34]. Theoretically, the use of iodine-125 with its 60-day half-life may be ideal for slowly dividing cell lines, but it may be inadequate for those prostate cancers that are rapidly dividing. This potential problem might be overcome with the development of new radioisotopes such as palladium-103, which has a half-life of only 17 days. As a result of these theoretical dose rate issues and laboratory investigations, some radiation oncologists are currently using iodine-125 for low grade gleason score prostate malignancies and palladium-103 for the higher grade gleason score malignancies. The result has been a renewed interest in brachytherapy and the dramatically increased use of outpatient closed transperineal permanent interstitial radioactive seed implantation.

There are many recent articles describing the specific techniques used by various centers [10,35–37]. Some use computerized tomography (CT) guidance [24]. Others use transrectal ultrasound (TRUS) guidance with or without fluoroscopy [8,9,14,17]. When TRUS prostate volumes are compared to CT prostate volumes, there is a difference in the apparent size of the prostate. The CT volume appears to overestimate the size of the prostate when compared to pathologic specimens, whereas the TRUS volume appears closely to approximate the prostatectomy prostate volume [38].

Currently, centers performing interstitial permanent brachytherapy perform conformal implants based on preplanning CT or TRUS volumetrics. The prostate volume is evaluated by taking 5 mm cuts with CT or TRUS. The planned treatment volume contours are entered into a treatment planning computer and a treatment plan is derived that will direct the three-dimensional configuration of the implant coordinates and the seed strength [9,11,14]. Most templates used to guide the implant use 1.0 or 0.5 cm spacing; thus the spacing of the seeds is usually 1.0 cm from seed center to seed center uniformly throughout the gland. Some centers weight the implant by using fewer seeds of higher average activity loaded more heavily in the periphery of the gland. Whether using peripheral or uniform loading, most centers use conformal computer generated preplans based on the size and shape of the individual patient's prostate instead of an idealized prostate volume.

At the time of implantation, the patient is placed in the lithotomy position. Either spinal or general anesthesia is used. The ultrasound probe is inserted into the rectum, visualizing the prostate and surrounding structures. Real-time TRUS, or fluoroscopy, is used to guide the implant based on the preimplant computer-generated conformal plan. During the procedure, preloaded needles containing radioactive seeds alternating with absorbable 5 mm suture are placed through the template, then perineum, and into the prostate. There it is visualized by TRUS or fluoroscopy and the seeds and spacers are deposited into the gland. Commercial applicators can be used to deposit the seeds at the appropriate spacing instead of preloaded needles, depending on physician preference.

There is a surprising amount of distortion and movement of the prostate during the implant procedure, which is well visualized when using TRUS guidance. There are variations in prostate stabilization techniques during the procedure. Some centers use a Foley catheter balloon, whereas others use barbed stabilization needles that attach to the template. There are also differences in the uniformity of the spacing of the radioisotopes within the prostate. Blasko et al. [11], Priestly and Beyer [35], and Kaye et al. [17] have utilized a uniform loading technique with a relatively high number of low strength seeds. This allows homogeneous dosimetry even if occasional seeds are not placed (or do not stay) in the ideal preplanned position [11]. Other centers use a peripherally weighted loading scheme with a fewer number of higher strength seeds in order to decrease the dose to the urethra in hopes of decreasing urethral complications [24,36]. With longer follow-up, we may see that the specific technique variations at different centers result in different local control rates and complication rates.

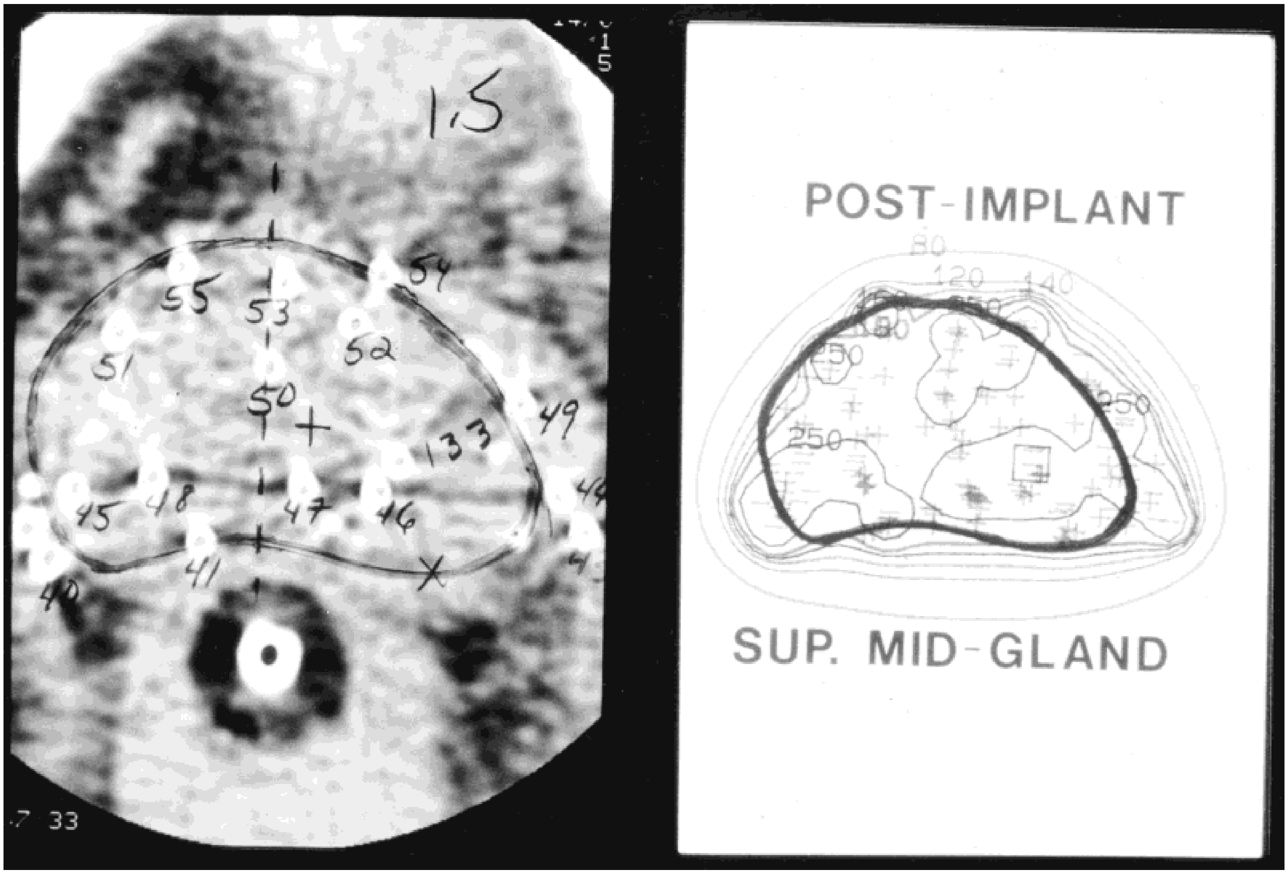

Fig. 3. Postimplant conformal planning CT and resulting brachytherapy isodose curves.

In patients whose disease has a low likelihood for microscopic extracapsular extension, implantation alone, with either iodine-125 (125-I) or palladium-103 (103-Pd), may be recommended. The doses are usually 160 Gy minimal peripheral dose (mpd) for 125-I, and 115 mpd for 103-Pd. In those patients with a high chance of microscopic extracapsular spread, some centers deliver 45 Gy external beam radiation therapy to the prostate, seminal vesicles, and periprostatic tissue or limited pelvis followed by a lower dose implant. For example, Blasko et al. [11] uses a ‘‘boost implant’’ dose of 120 Gy for 125-I and 90 Gy for 103-Pd following 45 Gy external beam to a limited pelvic field [11].

Following the implant, postimplant dosimetry is performed using a treatment planning CT with 5 mm cuts [10,15]. Although the CT may overestimate the size of the prostate it does allow one to evaluate the homogeneity of the implant in that particular patient (Fig. 3). Postimplantation dosimetric analysis is critical to an implant program. It points out to the radiation oncologist whether a particular region is consistently under- or overdosed, thus allowing the physician to make adjustments for this in future implants.

Temporary Interstitial Brachytherapy

Temporary implants have been performed with a limited course of external beam radiation therapy, as a boost. Iridium-192 (192-Ir) is the radioisotope used for temporary interstitial brachytherapy. Most studies have described the use of low dose rate 192-Ir. Early series required open laporotomy and did not use CT or TRUS guidance. This resulted in relatively high complication rates, which have decreased in recent years as improvements in technique and source strength and placement were developed [23,30,39–41]. In the past, the patient would undergo open laporotomy lymph node dissection and transperineal template guided placement of afterloading needles. The 192-Ir would be loaded into the needles at the patient’s bedside after treatment planning X-rays were taken to allow adjustments in loading to compensate for any malalignment in the positioning of the needles (Fig. 4). A few days later the needles and 192-Ir would be removed. The development of TRUS and high dose rate (HDR) 192-Ir machines has now allowed for closed temporary 192-Ir interstitial implantation [40,41]. Although hospitalization is still required, laporotomy is unnecessary and the needles are usually

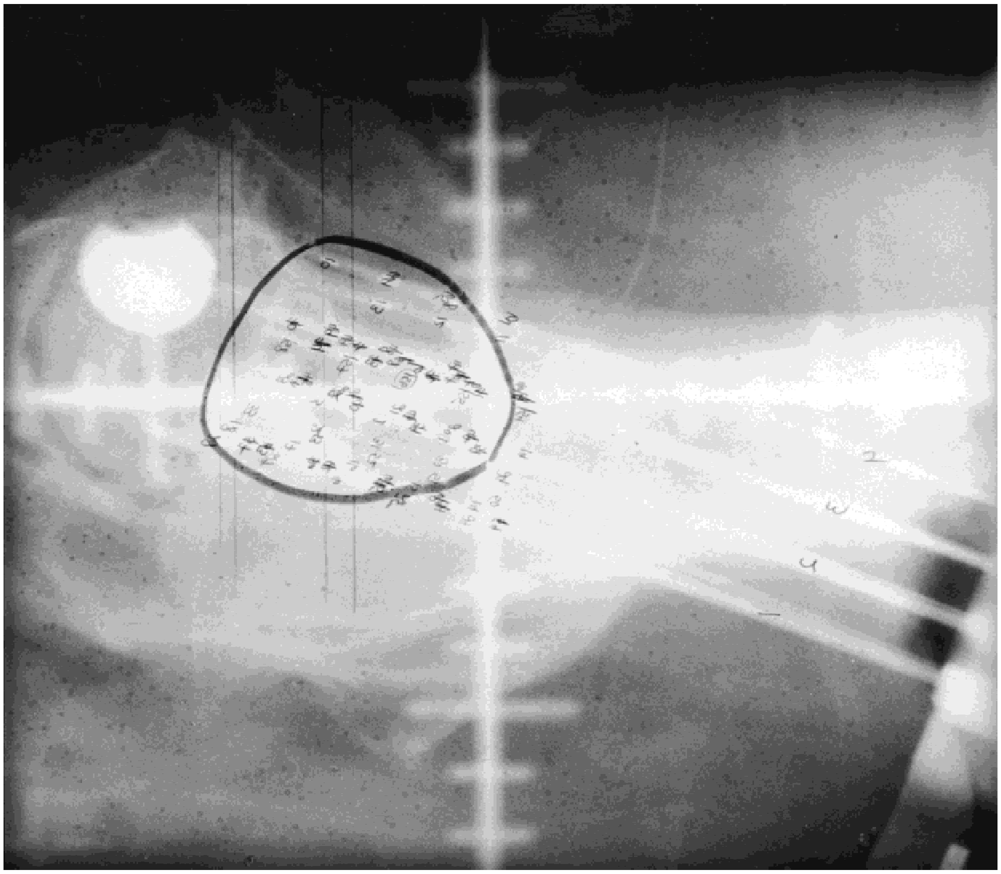

Fig. 4. Brachytherapy simulation film following temporary 192-Ir implant.

left in place for 2 days instead of 3. The HDR unit controls the temporary loading of the isotope by computer, allowing medical personnel to avoid any radiation exposure. The dose is given in minutes instead of hours; this high dose rate coupled with the higher penetration of 192-Ir (vs. 125-Id and 103-Pd) might increase the risk of damage to normal surrounding tissue, especially the rectum. There is little in the way of published data on results and toxicity with more than very short follow-up so far. This technology appears promising; the isodose curves can be shaped into proper orientation after the needles are inserted allowing the radiation oncologist to at least partially compensate for needles that may have been placed slightly out of the desired position.

CLINICAL RESULTS

Historical

The complication and overall survival rates of open retropubic permanent brachytherapy have been thoroughly reviewed in the literature. Debate continues as to the effectiveness of retropubic brachytherapy. Several centers treated patients with equivalent stage and grade prostate cancer with either 125-I brachytherapy or external beam radiotherapy comtemporarily. They have shown good survival data with each method [42–47]. Good survival does not necessarily credit the therapy. Prostate cancer often has a long natural history. Patients are often elderly with comorbid conditions. In the above studies, patients generally had low stage cancers. Thus a patient may have survived long enough to die of other causes despite poor implant dose homogeneity, limited external beam total dose, or disease extension beyond the confines of the area irradiated or surgically removed. Overall survival may not be the best test of the efficacy of local therapy. Evaluating the local control rate, the disease specific survival, posttreatment biopsy results, and the biochemical PSA progression-free survival reveals a clearer picture of the effectiveness of a particular therapy. Most of the data from the retropubic implantation era used digital rectal examination to define local control. Disease specific survival and PSA data were lacking.

A few centers have relatively long follow-up for retropubic 125-I implantation. Hilaris et al. [47] noted a >10-year survival of 70% in the subset of patients that were surgical candidates. These patients had solitary

TABLE I. Closed Transperineal Permanent Seed Implantation Results in Series Treating Stage T1 and T2 Prostate Cancer

Series	No. of patients	Initial median PSA[a]	Months of follow up (median)	Isotope	Local control	Distant disease-free survival	PSA results[a,b]
Priestly and Beyer [35]	480	7.3	35	I-125	83%	—	79% < 4.0 at 5 yr
Blasko et al. [55]	197	7.0	36	I-125	98%	98%	93% P-F at 5 yr
Kaye et al. [56]	45	11.0	24	I-125	—	—	98% < 4.0 at 2 yr
Wallner et al. [57]	62	9.0	19	I-125	95%	95%	83% P-F at 2 yr
Blasko et al. [13]	97	8.6	37	Pd-103	100%	95%	86% < 1.0 at 4 yr
Grado et al. [14]	241	11.3	24	I-125 or Pd-103	—	—	88% < 4.0 at 3 yr
Stock et al. [58]	97	—	18	I-125 or Pd-103	—	—	76% P-F at 2 yr

[a]Prostate specific antigen in ng/ml.
[b]P-F = Progression-free.

Jewett nodules and negative lymph node dissections. The overall survival was equivalent to the surgical literature and patterns of care external beam data of that era [47,48]. However, as the stage and grade of cancer increased, the local control rates of retropubic brachytherapy decreased [47]. The dose homogeneity was not always adequate in the free hand open retropubic implantation era. But when the implant was of good quality (⩾140 Gy mpd), the patient had stage A or early B and a well to moderately differentiated histologic grade, the local control rates were equal to external beam radiation [42]. These data helped increase the enthusiasm for brachytherapy. Modern brachytherapy built on the foundation of knowledge from the retropubic era.

Modern Brachytherapy Results

Modern brachytherapy has benefited from the technical advances discussed previously. Both CT and TRUS guided transperineal implantation appear to result in relatively homogeneous implants with mpds of at least 140 Gy for 125-I and 115 Gy 103-Pd when using implantation alone. Follow-up is <10 years, so most data are presented as PSA progression-free survival and local control, rather than overall survival. Postimplant biopsies have been performed at some centers as an additional method of local control evaluation. Controversy exists as to the meaning of a positive postradiation biopsy. Radiation damage is accumulated within the cell. It is not until after one or more divisions have taken place that cell death actually occurs. The timing of the biopsy, relative to treatment, can play a role in whether or not it is read as positive; it may take well over a year for cell death to become apparent on biopsy. Biopsies taken 12 months or less posttreatment can be misinterpreted as positive, when in actuality the cells have sustained lethal damage and are on the road to cellular death. Thus, biopsy should not be performed until 18–24 months after therapy [49–52].

Prostate specific, antigen monitoring posttreatment has become essential in assessing the status of the patient because it allows for earlier detection of failure than traditional endpoints [53,54]. A variety of PSA endpoints, following definitive radiation therapy, have been used in the literature. It is currently unresolved as to which endpoint is most appropriate. Some use PSA <4.0, others <1.0, and still others define control as a lack of PSA progression during follow up.

Results of Permanent Interstitial Implantation Alone

To date, there are no randomized prospective studies evaluating brachytherapy. All studies reported in the literature are single institution retrospective reviews. Some difficulty exists comparing contemporary series due to varying length of follow-up and different endpoint definitions. Comparing current brachytherapy series results to historical external beam series favors brachytherapy, since most current brachytherapy studies contain patients at an earlier stage of the disease. Current implant alone patients more closely resemble surgical series patients (early stage) than the traditional external beam radiation series in the pre-PSA era. Currently, patients are often diagnosed because an elevated PSA leads the primary care physician to refer the patient to the urologist for biopsy well before (perhaps years before) symptoms occur. The local control rates for modern brachytherapy vary depending on the stage of the patient at diagnosis and length of follow-up. Patients treated with interstitial brachytherapy alone (monotherapy) are usually earlier stage, because monotherapy would not be chosen if microscopic extracapsular disease was suspected. These earlier stage patients would be expected to have better control rates than later stage patients treated with implantation plus external beam. The local control and distant disease-free survivals are shown in Table I [13,14,35, 55–58]. It is difficult to compare results from different centers due to the different definitions of control chosen at the various centers and the different lengths of follow-up. Most series reporting used 125-Iodine on the lower gleason score tumors and 103-Palladium on the higher gleason score tumors, due to dose-rate concerns. The 103-Pd series have patients with higher grade lesions and

TABLE II. Biopsy Results After Interstitial Brachytherapy in Early Stage Prostate Cancer

Series	No. of patients	Isotope[a]	% Negative	% Indeterminate	% Positive
Blasko et al. [13]	53	103-Pd	87%	13%	0%
Kaye et al. [56]	41	125-I	51%	32%	17%
Prestidge et al. [50]	201	125-I/103-Pd	80%	17%	3%
Blasko et al. [12]	57	XRT + 103-Pd	78%	15%	7%
Kaye et al. [56]	20	XRT + 125-I	67%	13%	20%
Stromberg et al. [40]	10	XRT + 192-Ir HDR	90%	—	10%

[a]XRT = external beam irradiation; HDR = high dose rate brachytherapy.

thus a worse prognosis from the outset. The 83–100% local control rates at 2–5 years reported by brachytherapy centers appear superior to the recent external beam series [13,14,35,59,60].

Posttreatment biopsy data is limited to a few series thus far. As discussed previously, biopsies obtained too early may reveal cells with radiation damage but uncertain viability, i.e., an ‘‘indeterminate biopsy.’’ These initially indeterminate biopsies usually are found to be negative on biopsies taken 1 or more years later [50]. Overall, biopsy results are favorable, especially if most ‘‘indeterminate biopsies’’ convert to negative with further follow-up. Positive posttreatment biopsy rates are running between 0–10% in most current brachytherapy series (Table II) [12,13,40,50,56].

External Beam Radiation Plus Interstitial Brachytherapy Boost

In patients with a significant risk of microscopic extracapsular disease, monotherapy would be expected to have a high regional recurrence rate due to under dosing of this disease extension. Using external beam irradiation prior to the permanent implant, one might be able to sterilize this microscopic extension. A few series using this treatment plan have been published so far. The patients in these series have higher stage, higher pretreatment median PSA, and higher grade than most monotherapy or surgical trials. These patients’ profiles compare to recently published external beam series. These external beam series broke their results down by pretreatment PSA and followed the posttreatment PSA progressions [59,60]. Ideally one would want to compare the results of external beam versus implantation in a randomized study. Such a study does not exist, so one is left with comparison of modern contemporary retrospective studies instead, with all the associated pitfalls. The results of combined external beam and permanent interstitial brachytherapy appear to be providing good biochemical, PSA progression-free survival, and disease-free survival. Blasko et al. report a crude local control rate of 97%. With 5-year actuarial follow-up, they note 64% of patients treated have PSA levels <1.0 despite a mean initial PBS of 13.5 (Table III) [40,41,56,61]. The posttreatment biopsy data from several series reveal positive biopsies in only 7–20% (Table II). These results appear to be superior to recent external beam therapy alone data, particularly in patients with initial PSA levels between 10 and 20, based on intermediate follow-up and taking into account the problems of comparing retrospective series.

If boosting with temporary 192-Iridium (either low dose rate or HDR) external beam radiation could be given before or after the implant. Mate and Gottesman [41] and Stromberg et al. [40] have reported on external beam plus HDR. Mate and Gottesman [41] reported 84% of patients had PSA levels <4.0 at 3 years. Stromberg’s [40] results appear similar, with shorter follow-up (Table III). Stromberg [40] has noted that biopsies were positive in 10% of his patients after treatment.

Complications of Brachytherapy

Permanent interstitial implantation with 125-Iodine, 103-Palladium, and temporary 192-Iridium HDR brachytherapy have gained much attention in the media recently. Increased scrutiny of the complication rates is indicated, especially now that there are several different treatment options available to the patient with early stage disease. Current data reveal that patients can expect an increase in their pre-implantation symptoms of urinary obstruction and urethral irritation for several weeks to months following a permanent implant. These symptoms of urinary frequency, urgency, and dysuria are common but temporary in the vast majority of patients treated [62,63]. The permanent complications of monotherapy are more important and appear low as compared to surgery. The incontinence rates are quite low. Wallner et al. [57] reported no incontinence and a 10% incidence of genitourinary symptoms that required subsequent TURP. Priestly and Beyer [35] and Blasko et al. [61] report a 1–6% risk of incontinence overall, with longer follow-up. They use a uniform seed distribution technique that delivers a higher dose centrally than the mpd (Fig. 5). Patient selection appears important here. In patients with prior TURP, the risk of incontinence was 16% and superficial urethritis was 12%. However, patients without a history of TURP had an incontinence rate of 0% and superficial urethritis rats of only 0.4% [11]. Radiation proctitis rates vary from 2% in the series of Blasko et al. [61], to 12% in the series of Wallner et al. Wallner et al.

TABLE III. Clinical Results of Moderate Dose External Beam Irradiation Plus Transperineal Interstitial Brachytherapy Boost in Early Stage Prostate Cancer

Series	No. of patients	Initial median PSA[a]	Stage	Therapy[b]	No. of months follow-up (median)	Crude local control	Actuarial PSA[a] follow-up results
Blasko et al. [61]	57	13.5	T1-T3	XRT + 103-Pd	35	97%	64% < 1.0 at 5 yr
Kaye et al. [56]	31	12.6	T1-T2	XRT + 125-I	29	—	90% < 4.0 at 2 yr
Mate and Gottesman [41]	99	13.9[c]	T1-T3	XRT + 192-Ir HDR	28	—	84% < 4.0 at 3 yr
Stromberg et al. [40]	33	15.4	T2B-T3	XRT + 192-Ir HDR	13	—	92% < 4.0 at 1 yr

[a]Prostate specific antigen in ng/ml.
[b]XRT = external beam irradiation; HDR = high dose rate brachytherapy.
[c]mean.

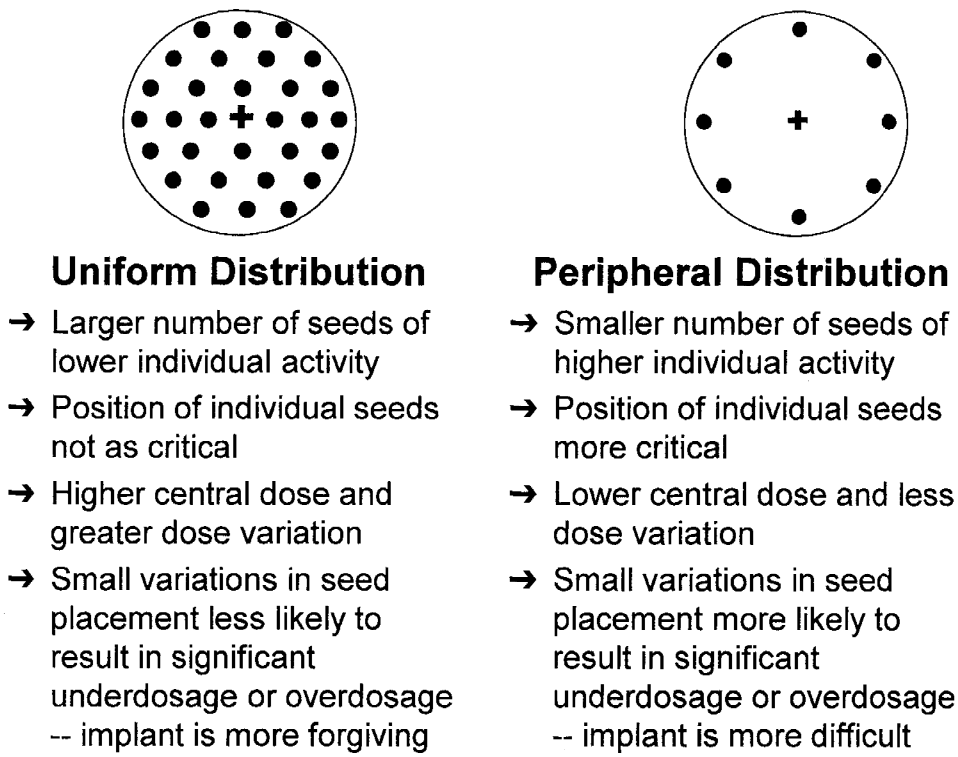

Fig. 5. Uniform versus peripheral permanent interstitial seed implantation.

[24] used the peripheral loading technique, which would be expected to deliver a higher dose to the anterior rectal wall than the uniform method used by Blasko et al. [11], Priestly and Beyer [35], and Kaye et al. [17]. Impotency rates are premature and vary somewhat among the different centers, but specifics regarding pre-implant functioning are sparse (Table IV) [35,36,41,56,57,63]. When using external beam and a permanent implant boost, the anterior rectal wall receives a higher dose than with monotherapy. Fortunately, the proctitis rate has increased only slightly as a result. In series using combination therapy with permanent implants, the implant is given after the completion of the external beam component to avoid irradiating tissue that has active radioactive sources. Two series used external beam after the permanent implantation and both had a high rate of complications. In the series reported by Critz et al. [64], the implant dose was only 80 Gy and the external beam was 45 Gy at 1.5 Gy per fraction; they noted a 15% proctitis rate. The series reported by Iverson et al. [65[used high dose per fraction to 47.4 Gy external beam after 160 Gy MPD; this resulted in a 42% severe complication rate. In series using temporary afterloading, the external beam can be given before or after the temporary implant boost. Data on complications using external beam with HDR boost with >2–3 years of follow-up are limited.

DISCUSSION

Prostate cancer has attracted the attention of both the media and the general population. Historically radical prostatetomy had been the gold standard. Much like

TABLE IV. Complications of Closed Transperineal Brachytherapy in Early Stage Prostate Cancer

Series	Therapy[a]	Incontinence[b]	Impotency	Radiation proctitis	Urinary retention	Urethritis
Priestly and Beyer [35]	125-I	1%	—	1%	—	4%
Blasko et al. [63]	125-I	TURP 17% non-TURP 0%	Age > 70–50% Age < 70–15%	2%	7%	7%
Wallner et al. [57]	125-I	0%	19%	12%	0%	—
Blasko et al. [63]	XRT + 125-I	TURP 13% non-TURP 0%	Age > 70–50% Age < 70–15%	6%	4%	4%
Kaye et al. [56]	125-I ± XRT	TURP 11% non-TURP 1%	25%	9%	5%	1%
Dattoli et al. [36]	XRT + 103-PD	1%	23%	—	7%	—
Mate and Gottesman [41]	XRT + 192-Ir HDR	0%	—	—	2%	—

[a]XRT = external beam irradiation; HDR = high dose rate brachytherapy.
[b]TURP = transureathral resection of the prostate.

breast cancer a decade ago, controversy exists as to the most appropriate therapy. Unlike breast cancer, there are no properly controlled randomized trials comparing current treatment modalities. With the use of PSA in follow-up, it is apparent that the control rates of radical prostatectomy and external beam irradiation are not as high as once was thought. Using PSA in follow-up of modern surgical and external beam radiation series has shown (with intermediate follow-up), that biochemical progression-free survival is similar between the two modalities when risk factors are taken into account [55,61]. The goal of any local therapy is to eliminate the local disease. The local control rate needs to be as high as possible, with acceptable morbidity, for a local therapy such as radiation or surgery to be of value. With intermediate follow-up, brachytherapy appears to provide excellent local control, based on biopsy and PSA data. In the modern PSA-era, it is reasonable to consider that neither surgery nor external beam therapy have more mature data than that published in the brachytherapy literature. Results from several centers show that patients with PSAs <15 ng/ml at the time of presentation, treated with permanent interstitial brachytherapy, have control rates equal or superior to any other modality thus far reported [13,14,55–57,61]. Although it appears promising, it is not known yet if the results of temporary hdr 192-Ir brachytherapy will be maintained with longer follow-up. It is not clear that the results reported on in the literature by a few dedicated high volume centers can be duplicated by other centers. Currently, it appears that brachytherapy is a reasonable treatment option in properly selected patients with stage T1 and T2 disease. What does appear to be clearly supported in both the urologic and radiation oncologic literature is that patients presenting with high (>15–20 ng/ml) PSA values usually fail biochemically even when there is no evidence for local failure. In these individuals, systemic therapy may be indicated, in addition to local therapy, if it can be demonstrated that systemic therapy is effective at preventing recurrence.

REFERENCES

1. Garfinkel L, Mushinski M: Cancer incidence, mortality and survival: Trends in four leading sites. Statisical Bull 1994;75(3):19–27.
2. Mettlin C, Jones GW, Murphy GP: Trends in prostate cancer care in the United States 1974–1990: Observations from the patient care evaluation studies of the American College of Surgeons Commission on Cancer. CA Cancer J Clin 1993;43:83–91.
3. Fleming C, Wasson JH, Albertsen PC, et al.: A decision analysis of alternative treatment strategies for clinically localized prostate cancer. JAMA 1993;269:2650–2658.
4. Litwin MS: Health-related quality of life after treatment of localized prostate cancer. Cancer 1995;75:2000–2003.
5. Talcott JA, Rieker P, Propert K, et al.: Complications of treatment of early prostate cancer. A prospective multi-institutional outcomes study. (abstract). Proc Am Soc Clin Onc 1994;13;A711.
6. Johansson J, Adami H, Anderson S, et al.: High 10 year survival rate in patients with early, untreated prostate cancer. JAMA 1992; 267:2191–2196.
7. Wingo PA, Tong T, Bolden S: Cancer Statistics, 1995. CA Cancer J Clin 1995;45:8–30.
8. Holm HH, Juul N, Pedersen JF, et al.: Transperineal I-125 seed implantation in prostatic cancer guided by transrectal ultrasonography. J Urol 1983;130:283–286.
9. Blasko JC, Ragde H, Schumacher D: Transperineal percutaneous iodine-125 implantation from prostatic carcinoma using transrectal ultrasound and template guidance. Endocurietherapy Hyperthermia Oncol 1987;3:131–139.
10. D'Amico AV, Coleman CN: Role of interstitial radiotherapy in the management of clinically organ-confined prostate cancer: The jury is still out. J Clin Oncol 1996;14:304–315.
11. Blasko JC, Grimm PD, Ragde H: Brachytherapy and organ preservation in the management of carcinoma of the prostate. Semin Radiat Oncol 1993;3:240–249.
12. Blasko JC, Grimm PD, Ragde H: External beam radiation with palladium-103 implantation for prostate carcinoma. Int J Radiat Oncol Biol Phys 1994;30:219.
13. Blasko JC, Ragde H, Grimm PD, et al.: Transperineal ultrasound guided palladium-103 brachytherapy for prostate carcinoma (abstract). J Urol 1995;153:385.
14. Grado GL, Larson TR, Collins JM, et al.: Fluoroscopic and ultrasound guided prostate implant: Technique and experience at Mayo Clinic Scottsdale (abstr), American Brachytherapy Society, 18th Annual Meeting. Scottsdale, Arizona 1995; (abstract) p 10.
15. Grimm PD, Blasko JC, Ragde H: Ultrasound-guided transperineal implantation of iodine-125 and palladium-103 for the treatment of early stage prostate cancer: technical concepts in planning, operative technique, and evaluation. In Schellhammer PF (ed): ''New Techniques in Prostate Surgery: Atlas of the Urologic Clinics of North America.'' Philadelphia: W.B. Saunders, 1994, pp 2:113–125.

16. Gore RM, Moss AA: Value of computed tomography in interstitial 125-I brachytherapy of prostatic carcinoma. Radiology 1983; 146:453–458.
17. Kaye KW, Olson DJ, Lightner DJ, et al.: Improved technique for prostate seed implantation: Combined ultrasound and fluoroscopic guidance. J Endourology 1992;6:61–66.
18. Porter AT, Blasko JC, Grimm PD, et al.: Brachytherapy for prostate cancer. CA Cancer J Clin 1995;45:165–178.
19. Ragde H, Blasko JC, Schumacher D, et al.: Use of transrectal ultrasound in transperineal Iodine-125 seeding for prostate cancer: Methodology. J Endourology 1989;3:209.
20. Roy JN, Ling CC, Wallner KE, et al.: Determining source strength and source distribution for a transperineal prostate implant. Endocurie/Hyperthermia Oncology 1996;12:35.
21. Roy JN, Wallner KE, Harrington PJ, et al.: A CT-based evaluation method for permanent implants: Application to prostate. Int J Radiat Oncol Biol Phys 1993;26:163–169.
22. Russell KJ, Blasko JC: Recent advances in interstitial brachytherapy for localized prostate cancer. In Lange P. (ed): ''Problems in Urology,'' vol. 7. Philadelphia: J.B. Lippincott, 1993, p 260–279.
23. Syed AM, Puthawala A, Austin P, et al.: Temporary Iridium-192 implant in management of carcinoma of the prostate. Cancer 1992;69:2515–2524.
24. Wallner KE, Chiu-Tsao S, Roy J, et al.: An improved method for computerized tomography-planned transperineal prostate implantation. J Urol 1991;146:90–95.
25. Wallner KE, Roy J, Zelefsky M, et al.: Flouroscopic visualization of the prostatic urethra to guide transperineal prostate implantation. Int J Radiat Oncol Biol Phys 1994;29:863–867.
26. Denning CL: Carcinoma of the prostate seminal vesicles treated with radium. Surg Gynecol Obstet 1922;34:99–118.
27. Scardino PT, Carlton CE: Combined interstitial and external irradiation for prostatic cancer. In Javadpour N (ed): ''Principles and Management of Urologic Cancer.'' Baltimore: Williams & Wilkins, 1983, p 392–408.
28. Whitmore WF Jr, Hilaris B, Grabstald H: Retropubic implantation of iodine 125 in the treatment of prostatic cancer. J Urol 1972; 108:918–920.
29. Anderson LL: Spacing nomograph for interstitial implants of I-125 seeds. Med Phys 1976;3:48–51.
30. Puthawala A, Syed AM, Tansey L: Temporary iridium-192 implant in the management of carcinoma of the prostate. Endocurietherapy Hyperthermia Oncology 1985;1:25–33.
31. Martinez A, Edmundsen GK, Cox RS, et al.: Combination of external beam irradiation and multiple-site perineal applicator (MUPIT) for the treatment of locally advanced or recurrent prostatic, anorectal, and gynecological malignancies. Int J Radiat Oncol Biol Phys 1985;11:391–398.
32. Wallner KE, Chiu-Tsao S, Roy J, et al.: A new device to stabilize templates for transperineal I-125 implants. Int J Radiat Oncol Biol Phys 1991;20:1075–1077.
33. Mitchell JB, Beford JS: Dose-rate effects in synchronous mammalian cells in culture. Radiat Res 1977;71:547–560.
34. Marchese MJ, Hall EJ: Encapsulated 125-Iodine in radiation oncology: II-P.L.D.R. and plateau phase cell cultures. Am J Clin Oncol 1984;7:613–616.
35. Priestly JB, Beyer DC: Guided brachytherapy for treatment of confined prostate cancer. Urology 1992;40:27–31.
36. Dattoli MJ, Wasserman SG, Kovall J, et al.: Conformal brachytherapy boost to external beam irradiation for localized high risk prostate cancer (abstr). Int J Radiat Oncol Biol Phys 1995;32: 251.
37. Stock RG, Stone NN, Wesson MF, et al.: A modified technique allowing interactive ultrasound guided three-dimensional transperineal implantation. Int J Radiat Oncol Biol Phys 1995;32:219–225.
38. Hastak SM, Gammelgaard J, Holm HH: Transrectal ultrasonic volume determination of the prostate: A preoperative and postoperative study. J Urology 1982;127:1115–1118.
39. Khan K, Thompson W, Bush S, et al.: Transperineal percutaneous iridium-192 interstitial template implant of the prostate: Results and complications in 321 patients. Int J Radiat Oncol Biol Phys 1992;22:935–939.
40. Stromberg J, Martinez A, Gonzalez J, et al.: Ultrasound-guided high dose rate conformal brachytherapy boost in prostate cancer: Treatment description and preliminary results of a phase I/II clinical trial. Int J Radiat Oncol Biol Phys 1995;33:161–171.
41. Mate TP, Gottesman J: Fractionated HDR conformal prostate brachytherapy. (abstr.), 8th International Brachytherapy Conference. Nice, France, Nov 1995.
42. Fuks Z, Leibel SA, Wallner KE, et al.: The effect of local control on metastatic dissemination in carcinoma of the prostate: Long-term results in patients treated with I-125 implantation. Int J Radiat Oncol Biol Phys 1991;21:537–547.
43. Giles GM, Brady LW: I-125 implantation after lymphadenectomy in early carcinoma of the prostate. Int J Radiat Oncol Biol Phys 1986;12:2117–2125.
44. Kuban DA, El-Mahdi AM, Schellhammer PF: I-125 interstitial implantation for prostate cancer: what have we learned 10 years later? Cancer 1989;63:2415–2420.
45. Morton JD, Peschel RE: Iodine-125 implants verus external beam therapy stages A2, B, and C prostate cancer. Int J Radiat Oncol Biol Phys 1988;14:1153–1157.
46. Schellhammer PF, Whitmore WF, Kuban DA, et al.: Morbidity and mortality of local failure after definative therapy for prostate cancer. J Urol 1989;141:567–571.
47. Hilaris BS, Fuks Z, Nori D, et al.: Interstitial irradiation in prostate cancer: Report of ten-year results. In Rolf S (ed): ''Interventional Radiation Therapy: Techniques/Brachytherapy.'' New York: Springer-Verlag, 1991, p 235–240.
48. Hanks GE, Leibel SA, Krell JM, et al.: Patterns of care studies: Dose-response observations for local control of adenocarcinoma of the prostate. Int J Radiat Oncol Biol Phys 1985;11:153–157.
49. Mostofi FK, Sesterhan IA, Davis CJ: A pathologist's view of prostatic carcinoma. Cancer (suppl) 1993;71:906.
50. Prestidge BR, Hoak DC, Grimm PD, et al.: Post-treatment biopsy results following interstitial brachytherapy in early stage prostate cancer. Int J Radiat Oncol Biol Phys 1997;37:31–39.
51. Scardino PT: The prognostic significance of biopsies after radiotherapy for prostate cancer. Semin Urol 1983;1:243–252.
52. Schellhammer PF, El-Mahdi AM, Higgins EM, et al.: Prostate biopsy after definative treatment by interstitial 125-Iodine implant or external beam radiation therapy. J Urol 1987;137:897–901.
53. Lange P, Ercole C, Lightner D, et al.: The value of serum prostate specific antigen determinations before and after radical prostatectomy. J Urol 1989;141:873–879.
54. Pollack A, Zagars GK, Kavadi VS: Prostate specific antigen doubling time and disease relapse after radiotherapy for prostate cancer. Cancer 1994;74:670–678.
55. Blasko JC, Wallner K, Grimm PD, et al.: Prostate specific antigen based disease control following ultrasound guided 125-iodine implantation for stage T1/T2 prostatic carcinoma. J Urol 1995;154: 1096–1099.
56. Kaye KW, Olson DJ, Payne JT: Detailed preliminary analysis of 125-Iodine implantation for localized prostate cancer using percutaneous approach. J Urol 1995;153:1020–1025.
57. Wallner K, Roy J, Zelefsky M, et al.: Short-term freedom from disease progression after I-125 prostate implantation. Int J Radiat Oncol Biol Phys 1994;30:405–409.
58. Stock PG, Stone NN, DeWyngaert JK: PSA findings and biopsy results following interactive ultrasound guided transperineal brachytherapy for early stage prostate cancer. In Proceedings of the American Radium Society 78th Annual Meeting, Paris, France, 1995, p 58.
59. Zagars GK: Prostate specific antigen as a prognostic factor for prostate cancer treated by external beam radiotherapy. Int J Radiat Oncol Biol Phys 1992;23:47–53.
60. Zietman AL, Coen JJ, Shipley WU, et al.: Radical radiation therapy in the management of prostatic adenocarcinoma: The intial prostate specific antigen value as a predictor of treatment outcome. J Urol 1994;151:640–645.

61. Blasko JC, Ragde HH, Cavanagh W, et al.: Long term outcomes of external beam irradiation and I-125/Pd-103 brachytherapy boost for prostate cancer. Int J Radiat Oncol Biol Phys (submitted), 1996.
62. Arterbery VE, Wallner KE, Roy J, et al.: Short-term morbidity from CT-planned transperineal I-125 prostate implants. Int J Rad Oncol Biol Phys 1993;25:661–667.
63. Blasko JC, Radge H, Grimm PD: Transperineal ultrasound-guided implantation of the prostate: Morbidity and complications. Scand J Urol Nephrol 1991;137:113–118 (suppl).
64. Critz FA, Tarlton RS, Holladay DA: Prostate specific antigen-monitored combination radiotherapy for patients with prostate cancer. Cancer 1995;75:2383–2391.
65. Iversen P, Bak M, Juul N, et al.: Ultrasonically guided 125-Iodine seed implantation with external radiation in the management of localized prostatic carcinoma. Urology 1989;XXXIV:181–185.